DEPARTMENT OF VETERANS AFFAIRS
Veterans Health Administration
Washington DC 20420

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UNDER SECRETARY FOR HEALTH'S INFORMATION LETTER

EXPOSURE TO HAZARDOUS DRUGS

1. Purpose. This Information Letter is to remind facilities of Federal Guidelines and Regulations regarding hazardous drug exposures and disposal at Department of Veterans Affairs (VA) facilities.

2. Definition. A hazardous drug is considered to be any pharmaceutical agent with the potential to cause increased risk of cancer, developmental or reproductive toxicity, or target organ effect in animal or human studies.

3. Background. A number of pharmaceuticals in the health care setting may pose occupational risk to VA staff through acute and chronic workplace exposure.

a. Past attention focused on antineoplastic drugs; however, many other agents also have toxicity profiles of concern. Antineoplastic drugs include chemically unrelated classes of agents capable of treating neoplasms by inhibiting tumor or cell growth. However, all antineoplastic drugs are not cytotoxic. Cytotoxic refers to an agent that may be genotoxic, oncogenic, mutogenic or teratogenic.

b. Identifying potentially hazardous drugs requires complex research and clinical skills. Resources are available to assist in the recognition of known hazardous drugs, personal protection techniques, and engineering controls for reducing potential exposure. The National Institutes of Occupational Safety and Health (NIOSH) has released a pre-publication NIOSH Alert, *Preventing Occupational Exposures to Antineoplastic and Other Hazardous Drugs in Healthcare Settings.* ***NOTE:*** *The final document is expected to be published in 2005, at which time the Occupation Safety and Health Administration (OSHA) and the American Society of Health-System Pharmacists (ASHP) may consider further revisions of regulations and recommendations.*

c. Virtually all drugs have side effects, and health care employees are at risk for experiencing these effects during drug preparation and administration. Acute symptoms may include dizziness, nausea, headache, and mucous membrane irritation. These symptoms have been reported immediately following skin contact with hazardous drugs.

(1) Studies have shown a positive association between hazardous drug exposure and reproductive health effects. Adverse reproductive health effects may include fetal loss, infertility, congenital malformations, and abnormalities. Some studies have also shown a

significant increased risk of leukemia and other cancers for pharmacy and nursing staff. Studies showing such results were generally conducted before the correct work practice and engineering controls were in place.

(2) Guidelines for work practices in the safe handling of hazardous drugs have long been available, but adherence to the guidelines has not always been consistent. Furthermore, detectable levels of drug contamination continue to be identified in health care facilities. Recent NIOSH guidance draws attention to the limits of biological safety cabinets (BSC) in controlling drug exposure, marginal use of personal protection by health care workers, and secondary exposure sources requiring greater controls for non-clinical staff.

d. The goals of a VHA hazardous drug program need to include:

(1) Protecting and securing packages of hazardous drugs;

(2) Educating VHA staff about hazardous drugs and safe handling procedures;

(3) Controlling the release of hazardous drugs during preparation, transfer, and administration; and

(4) Eliminating ingestion, inhalation, and eye or skin contact.

4. Determination of Hazardous Drugs and Exposure. Drugs are regulated by the United States (U.S.) Food and Drug Administration (FDA) and are covered by the OSHA Hazard Communication Standard (Title 29 Code of Federal Regulations (CFR) 1910.1200). However, 29 CFR 1910.1200 section (b)(6)(viii) exempts FDA drugs when in solid final form, such as tablets or pills, for direct administration to the patient. The drug manufacturer or distributor is responsible for conducting the hazard determination based upon the criteria specified in the OSHA standard. If there is any question regarding a drug hazard, the drug manufacturer needs to be contacted for clarification. As part of OSHA Hazard Communication compliance, facility safety managers need to maintain a list of facility hazardous drugs, ensure a process for the identification of new hazards, and be aware of the availability of drug hazard information, employee training, and spill response.

a. Hazardous drug lists are reviewed and updated annually by NIOSH and the National Institutes of Health (NIH). Some antineoplastic drugs have also been classified by the International Agency for Research on Cancer (IARC) as cancer-causing agents. Antineoplastic drugs are designated as Therapeutic Category 10:00 under American Hospital Formulary Service, Drug Information (AHFS). In addition to the formal listing, the NIOSH recommendations for handling hazardous drugs need to be utilized for any drug that documents carcinogenicity, genotoxicity, teratogenicity, or reproductive and developmental toxicity in the Material Safety Data Sheet (MSDS) or package insert. OSHA, NIOSH, and NIH hazardous drug lists are available at the VHA Center for Engineering and Occupational Safety and Health (CEOSH) web site: http://vaww.ceosh.med.va.gov.

b. Traditional industrial hygiene airborne exposure limits for hazardous drugs are generally not available. Drug manufacturers may have developed permissible exposure limits during processing. As an example, the pharmaceutical industry has developed an employee airborne exposure limit of 10 micrograms per cubic meter of air (10 mcg/M^3) for drugs shown to produce toxic effects in laboratory animals administered at a daily rate of 1 milligram per kilogram of animal weight (1mg/Kg/day). In some instances, air sampling methodology for hazardous drugs must address both particulate and vapor phases during drug handling and use. No single biomarker has surfaced as a predictor of exposure, although the detection of urinary alkylating agents, specific drugs, and metabolites in health care workers has been well documented, even when good work practices were determined to be in place.

5. <u>Exposure Pathways.</u> Exposure to hazardous drugs occurs mainly by inhalation and skin absorption, and secondarily by ingestion and sharps injury. Administration of drugs via aerosolization (i.e., ribavirin, pentamidine) without proper controls can lead to measurable air concentrations in the breathing zone of health care staff. More comprehensive exposure sampling surveys have shown low or no measurable airborne concentration levels, and in some cases widespread surface contamination. At one time, improper engineering controls and work practices ("clean-air" benches, bedside intravenous (IV) preparation) contributed to sustained exposures and the development of chronic disease among health care workers. Current studies now identify the potential for low-background exposures and the occurrence of one-time events (Intravenous (IV) leak, spill response, excreta exposure) as the predominant exposure events.

a. Factors affecting the level of staff exposure include: the amount and concentration of drug; type of drug handling task (preparation, administration or disposal); the frequency and duration of the task; and the drug potential for skin adsorption or inhalation. ***NOTE:*** *The level of applied protective engineering and work practice controls are the primary determinants of staff exposure levels.*

b. Hazardous drugs need to be controlled at the point of facility entry. The most significant risk during receipt involves spills from damaged packaging or improper handling. During drug preparation and administration, a variety of manipulations are performed that may result in the generation of airborne drug particles, aerosols, and vapor. Examples of these manipulations include: pulverizing, priming IV tubing, the withdrawal of needles from drug vials, use of syringes for drug transfer, the opening of ampules, and the expulsion of air from the syringe. Staff may also be exposed when handling contaminated equipment and supplies during these processes. Hazardous drug exposure has also been shown to occur from patient excreta during therapy, including the handling of contaminated linens and patient room surfaces. ***NOTE:*** *There is an increasing concern for exposure of family members during home care and drug administration.*

6. <u>Recommended Work Practices and Personal Protection.</u> Written safe work procedures need to be established and developed from existing OSHA, NIOSH, and ASHP standards and recommendations. VA staff assigned to handling, mixing, or administration of hazardous drugs need to be trained in: standard safe work procedures, the hazards of antineoplastic and cytotoxic drugs, the risk of exposure, and proper spill procedures.

a. Hazardous drugs need to be fully labelled and transported in secondary-closed containers to prevent exposure during impact or abusive handling. Staff transporting hazardous drugs need to be trained in: the recognition of warning labels, damaged packaging, spill site control, and reporting.

b. Hazardous drug preparation and IV priming need to be conducted in a Class II or III BSC. Work surfaces need to be covered with disposable paper, and the underlying and surrounding surface cleaned at the end of the work shift. Double gloves (nitrile or non-latex) are recommended with protective gowns. The gown needs to have low permeability with a closed front and long sleeves. The inner glove needs to extend under the gown cuff and the outer glove extends over the cuff. For extended exposures, disposable sleeve covers need to be worn over the glove-gown ensemble. ASHP also recommends that gloves be changed every 30 minutes or when torn, punctured, or contaminated. Hands need to be washed with soap and water upon removal of gloves and protective clothing. Final products and devices need to be wiped and placed in sealed containers that are labelled for transport to the administration site.

c. Safe administration of hazardous drugs may include the use of needleless systems, closed systems (Phaseal) or in-line priming with non-drug solutions. Personal protective equipment (PPE) needs to include the use of double gloves and gowns, as described in subparagraph 3a(2). Face shields or goggles are recommended during administration. A plastic-backed absorbent liner should be used to protect the work area in case of a spill or leak. PPE needs to be utilized during bag opening, system assembly, drug delivery, and system disposal. If possible, priming of IV tubing and syringes need to be done by the pharmacy in a Class II BSC. Syringes and IV sets should utilize Luer-Lok^{TM} fittings (dry) and connections that can be taped for added security. Over- or under-pressurization of IV sets and mishandling the IV bag or tubing connection may result in the release of a hazardous drug. Following therapy, the outer gloves and gown need to be removed and bagged with disposed equipment into a waste container. All waste needs to be fully contained prior to removal of the inner gloves. Hands need to be washed with soap and water after removing the inner gloves and prior to leaving the administration site.

d. Specific training in recognition and handling procedures needs to include housekeeping, laundry, and custodial staff. Contractors need to be informed of worksite hazards. Training needs to include the potential hazards of handling contaminated laundry, sources of exposure to excreta during therapy, area contamination of hazardous drugs, and safe work procedures when handling these materials. Staff handling contaminated linens (excreta, vomit, or blood) need to utilize double gloves and gown protection for a minimum of 48 hours following patient therapy.

e. Bathroom cleaning and excreta disposal procedures need to be developed to reduce exposure to aerosols and contact with contaminated surfaces. As a minimum, nitrile gloves need to be worn. Any clothing contaminated with patient excreta needs to be included with contaminated linens for cleaning. Face shields or eye goggles and disposable gowns need to be worn where splashing is possible.

7. BSCs. Transfer of hazardous drugs from primary packaging to dosing equipment needs to be conducted in Class II or III BSCs.

a. A Class II BSC provides product, personal, and environmental protection for the aseptic preparation of hazardous drugs. This is accomplished by filtering incoming and exhaust air through a high-efficiency particulate air (HEPA) filter. HEPA filters are rated for a minimum particulate removal of 99.97 percent for thermally-generated monodisperse dioctylphthalate (DOP) smoke particles with a diameter of 0.3 um (0.3 micron). ***NOTE:*** *HEPA filters are not effective for volatile materials because they do not capture vapors and gases.*

(1) Class II BSCs need to be certified every 6 months using the manufacturer recommendations or National Sanitation Foundation, Standard 49, Class II (Laminar Flow) Biosafety Cabinetry. Certification needs to include air velocity measurements and aerosol test of the exhaust HEPA filter. Replacement of HEPA filters needs to be done in a manner to prevent area contamination by using a glove bag method, while wearing protective gloves, clothing, and Type C respiratory protection. Used HEPA filters need to be discarded as chemotherapy waste.

(2) Although closed-system drug preparation is a recognized procedure (glovebags and system transfer devices), additional precautions are recommended. A decrease in drug contamination has been shown when a closed-system transfer device is used in a Class II BSC. A closed-system transfer is not generally considered an acceptable substitute for a Class II BSC unless additional safeguards are applied. Depending on the drug and process, these safeguards must include negative room pressurization, dedicated 100 percent exhaust ventilation or Type C respiratory protection.

b. Class III BSCs are totally enclosed, ventilated cabinets of gas-tight construction. Operations in the cabinets are conducted through attached rubber gloves. The cabinet is maintained under negative air pressure of at least 120 Pa (0.50 inch water gauge (wg)). Supply air is drawn into the cabinet through HEPA filters. The exhaust air is treated by double HEPA filtration, or by HEPA filtration and incineration. Class III BSCs are suitable for work with agents assigned to Biosafety Levels 1, 2, 3, and 4. Recently, the United States Pharmacopeia (USP) Chapter 797 required that work practices be classified as low, medium. and high-risk, and require the use of the International Organization for Standardization (ISO) Class 5 cabinets (Class II) and ISO Class 8 cleanroom environments. Class III gloveboxes, barrier isolators, or Mobile Isolation Chambers (MIC Units) can also be used to meet USP requirements for sterile preparation.

8. Spill Response and Waste Disposal. Consideration needs to be given to the development of a hazardous drug spill management team to include pharmacy staff expertise. All personnel likely to handle hazardous drugs need to be trained in facility spill management policy, practices to reduce the likelihood of spills, adverse event reporting procedures, and use of PPE. All hazardous drug waste needs to be disposed of in yellow or white chemotherapy containers, in accordance with the Environmental Protection Agency (EPA) Resource Conservation and Recovery Act (RCRA) and State regulations. RCRA, as enforced by EPA and authorized under State programs, regulates the disposal of solid wastes. A number of drugs are P- or U-Listed

hazardous waste under RCRA regulations (40 CFR Part 261); additionally, seven antineoplastic drugs (*) are U-Listed. Although a drug may meet the EPA-RCRA definition of a hazardous waste, NIOSH, OSHA, and NIH may not list it as a hazardous drug (cytotoxic).

a. Table 1 provides a list of pharmaceuticals that are P- and U-Listed.

Table 1. – RCRA P-Listed and U-Listed Pharmaceuticals
* Antineoplastic drugs

NAME	EPA HAZARDOUS WASTE NUMBER
Chlorambucil*	U035
Cyclophosphamide*	U058
Daunomycin*	U059
Melphalan*	U150
Mitomycin C*	U010
Streptozotocin*	U206
Uracil Mustard*	U237
Diethylstilbestrol	U089
Hexachlorophene	U132
Phenacetin	U187
Reserpine	U200
Resorcinol	U201
Saccharin	U202
Selenium Sulfide	U205
Warfarin <0.3 percent	U248
Arsenic Trioxide	P012
Epinephrine	P042
Nicotine	P075
Nitroglycerin	P081
Phentermine (CIV)	P046
Physostigmine	P204
Physostigmine Salicylate	P188
Warfarin > 0.3 percent	P001

b. The following chemicals (Table 2) may also be present in pharmaceutical formulations and cause drug waste to exhibit RCRA toxicity characteristics when present in concentrations at or above the indicated regulatory level. ***NOTE:*** *Refer to 40 CFR 261.24, Toxicity Characteristics, for a complete list of all forty chemicals and their regulatory limit.*

Table 2. RCRA Regulatory Levels for Pharmaceuticals

NAME	EPA HAZARDOUS WASTE NUMBER	REGULATORY LEVEL Milligrams per Liter (mg/L)
Arsenic	D004	5.0
Barium	D005	100.0
Cadmium	D006	1.0
Chloroform	D022	6.0
M-Cresol	D024	200.0
Lindane	D013	0.4
Mercury	D009	0.2
Silver	D011	5.0

c. Managing pharmaceutical waste streams are a challenge and represent P-, U- and D-Listed waste, in addition to ignitable waste (i.e., >24 alcohol) and toxic hazardous waste. A number of states consider all antineoplastic drugs (AHFS Therapeutic Category 10:00) without RCRA listing as State-regulated hazardous waste and prohibit inclusion with infectious waste. The concern is that infectious waste treatment is not an effective method for deactivating base compounds. Other states require segregation of chemotherapy waste into trace and bulk waste streams, and allow trace chemotherapy waste to be disposed of as infectious waste. Trace wastes are completely empty vials, bags, tubing, routine protective clothing, wipes, and surface pads that were not used to address a spill or drug release event. Bulk waste may be considered contaminated supplies from spill response, in addition to expired or unused drug products and IV sets.

d. Expired drugs in their original packaging are generally not considered hazardous waste and may be returnable to the drug manufacturer or distributor. Some states also consider expired drugs that have been returned back to the facility (not accepted by the manufacturer) as hazardous waste. VA medical center staff should become familiar with their state laws regarding disposal of hazardous wastes. EPA considers an outdated drug to remain a product (not classified a waste) until the decision has been made by the facility or distributor to discard it. Several resources further addressing these RCRA issues are provided on the VHA CEOSH website at: http://vaww.ceosh.med.va.gov.

9. Medical Surveillance. OSHA and professional organizations recommend medical surveillance for health care employees handling hazardous drugs. Employees who process or administer hazardous drugs on a daily or routine basis, respond to hazardous drug spills, or handle contaminated linens on a routine basis need to be included. A pre-placement medical exam needs to include a review of job duties, exposure history, and PPE. Evaluation for respirator use may be required for some employees. Periodic medical examinations may be conducted every 1-3 years depending upon any current exposure events. These examinations need to include education and awareness assessment. Post-exposure examinations may be conducted for all employees reporting symptoms following an exposure event, such as a spill or needlestick. Employees, who are pregnant, planning on becoming pregnant, or lactating should

be reminded of the program elements. No risk of increased hazard is expected when program elements are followed, but employees should know that attention to program adherence is important to ensure that systems remain in good working order.

10. References

a. Preventing Occupational Exposures to Antineoplastic and other Hazardous Drugs in Healthcare Settings, NIOSH, May 2004.

b. Technical Assistance Bulletin on Handling Cytotoxic and Hazardous Drugs, American Society of Health-System Pharmacists, ASHP,1990; 47:1033-49.

c. EPA Pharmaceuticals and Personal Care Products (PPCPs) in the Environment http://www.epa.gov/nerlesd1/chemistry/pharma/index.htm.

d. Handbook for the Management of Hazardous Waste, see http://vaww.ceosh.med.va.gov

e. National Sanitation Foundation, Standard 49, Class II (Laminar Flow) Biohazard Cabinetry, 2004.

f. The ASHP discussion Guide for Compounding Sterile Preparations, Summary of USP Chapter 797United States Pharmacopeia.

11. Contact. Questions regarding this information letter may be addressed to Network Program Support (10NB) at (202) 273-5870.

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Acting Under Secretary for Health

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